

We claim:

1. A peptide compound of the formula (I) [SEQ. ID. NO. 4]:

Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Gly Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub>  
Xaa<sub>11</sub> Xaa<sub>12</sub> Xaa<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>15</sub> Xaa<sub>16</sub> Xaa<sub>17</sub> Ala Xaa<sub>19</sub> Xaa<sub>20</sub>  
Xaa<sub>21</sub> Xaa<sub>22</sub> Xaa<sub>23</sub> Xaa<sub>24</sub> Xaa<sub>25</sub> Xaa<sub>26</sub> Xaa<sub>27</sub> Xaa<sub>28</sub>-Z<sub>1</sub>; wherein

Xaa<sub>1</sub> is His, Arg or Tyr;

Xaa<sub>2</sub> is Ser, Gly, Ala or Thr;

Xaa<sub>3</sub> is Asp or Glu;

Xaa<sub>5</sub> is Ala or Thr;

Xaa<sub>6</sub> is Ala, Phe, Tyr or naphthylalanine;

Xaa<sub>7</sub> is Thr or Ser;

Xaa<sub>8</sub> is Ala, Ser or Thr;

Xaa<sub>9</sub> is Asp or Glu;

Xaa<sub>10</sub> is Ala, Leu, Ile, Val, pentylglycine or Met;

Xaa<sub>11</sub> is Ala or Ser;

Xaa<sub>12</sub> is Ala or Lys;

Xaa<sub>13</sub> is Ala or Gln;

Xaa<sub>14</sub> is Ala, Leu, Ile, pentylglycine, Val or Met;

Xaa<sub>15</sub> is Ala or Glu;

Xaa<sub>16</sub> is Ala or Glu;

Xaa<sub>17</sub> is Ala or Glu;

Xaa<sub>19</sub> is Ala or Val;

Xaa<sub>20</sub> is Ala or Arg;

Xaa<sub>21</sub> is Ala or Leu;

Xaa<sub>22</sub> is Phe, Tyr or naphthylalanine;

Xaa<sub>23</sub> is Ile, Val, Leu, pentylglycine, tert-butylglycine  
or Met;

Xaa<sub>24</sub> is Ala, Glu or Asp;

Xaa<sub>25</sub> is Ala, Trp, Phe, Tyr or naphthylalanine;

Xaa<sub>26</sub> is Ala or Leu;

Xaa<sub>27</sub> is Ala or Lys;

Xaa<sub>28</sub> is Ala or Asn;

Z<sub>1</sub> is -OH,

-NH<sub>2</sub>,

Gly-Z<sub>2</sub>,

Gly Gly -Z<sub>2</sub>

Gly Gly Xaa<sub>31</sub>-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser Gly-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub>-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub> Xaa<sub>37</sub>-Z<sub>2</sub> or

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub> Xaa<sub>37</sub> Xaa<sub>38</sub>-Z<sub>2</sub>;

wherein

Xaa<sub>31</sub>, Xaa<sub>36</sub>, Xaa<sub>37</sub> and Xaa<sub>38</sub> are independently selected from the group consisting of Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine and N-alkylalanine; and

Z<sub>2</sub> is -OH or -NH<sub>2</sub>;

provided that no more than three of Xaa<sub>3</sub>, Xaa<sub>5</sub>, Xaa<sub>6</sub>, Xaa<sub>8</sub>, Xaa<sub>10</sub>, Xaa<sub>11</sub>, Xaa<sub>12</sub>, Xaa<sub>13</sub>, Xaa<sub>14</sub>, Xaa<sub>15</sub>, Xaa<sub>16</sub>, Xaa<sub>17</sub>, Xaa<sub>19</sub>, Xaa<sub>20</sub>, Xaa<sub>21</sub>, Xaa<sub>24</sub>, Xaa<sub>25</sub>, Xaa<sub>26</sub>, Xaa<sub>27</sub>, and Xaa<sub>28</sub> are Ala; and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein Xaa<sub>1</sub> is His or Tyr.

3. A compound according to claim 2 wherein Xaa<sub>1</sub> is His.
4. A compound according to claim 2 wherein Xaa<sub>2</sub> is Gly.
5. A compound according to claim 4 wherein Xaa<sub>14</sub> is Leu, pentylglycine or Met.
6. A compound according to claim 5 wherein Xaa<sub>25</sub> is Trp or Phe.
7. A compound according to claim 6 wherein Xaa<sub>6</sub> is Phe or naphthylalanine; and Xaa<sub>22</sub> is Phe or naphthylalanine; Xaa<sub>23</sub> is Ile or Val.
8. A compound according to claim 7 wherein Z<sub>1</sub> is -NH<sub>2</sub>.
9. A compound according to claim 7 wherein Xaa<sub>31</sub>, Xaa<sub>36</sub>, Xaa<sub>37</sub> and Xaa<sub>38</sub> are independently selected from the group consisting of Pro, homoproline, thioproline and N-alkylalanine.
10. A compound according to claim 9 wherein Z<sub>2</sub> is -NH<sub>2</sub>.
11. A compound according to claim 1 wherein Xaa<sub>2</sub> is Gly.
12. A compound according to claim 1 wherein Xaa<sub>14</sub> is Leu, pentylglycine or Met.
13. A compound according to claim 1 wherein Xaa<sub>25</sub> is Trp or Phe.
14. A compound according to claim 1 wherein Xaa<sub>6</sub> is Phē or naphthylalanine; Xaa<sub>22</sub> is Phe or naphthylalanine; Xaa<sub>23</sub> is

Ile or Val.

15. A compound according to claim 1 wherein  $Z_1$  is  $-NH_2$ .

16. A compound according to claim 1 wherein  $Xaa_{31}$ ,  $Xaa_{36}$ ,  $Xaa_{37}$  and  $Xaa_{38}$  are independently selected from the group consisting of Pro, homoproline, thioproline and N-alkylalanine.

17. A compound according to claim 1 wherein  $Z_2$  is  $-NH_2$ .

18. A compound according to claim 1 which has an amino acid sequence selected from SEQ. ID. NOS. 5 to 65.

19. A peptide compound of the formula (I) [SEQ. ID. NO. 4]:

$Xaa_1$   $Xaa_2$   $Xaa_3$  Gly  $Xaa_5$   $Xaa_6$   $Xaa_7$   $Xaa_8$   $Xaa_9$   $Xaa_{10}$   
 $Xaa_{11}$   $Xaa_{12}$   $Xaa_{13}$   $Xaa_{14}$   $Xaa_{15}$   $Xaa_{16}$   $Xaa_{17}$  Ala  $Xaa_{18}$   $Xaa_{19}$   
 $Xaa_{20}$   $Xaa_{21}$   $Xaa_{22}$   $Xaa_{23}$   $Xaa_{24}$   $Xaa_{25}$   $Xaa_{26}$   $Xaa_{27}$   $Xaa_{28}-Z_1$ ;

wherein

$Xaa_1$  is His or Arg;

$Xaa_2$  is Gly or Ala;

$Xaa_3$  is Asp or Glu;

$Xaa_5$  is Ala or Thr;

$Xaa_6$  is Ala, Phe or naphthylalanine;

$Xaa_7$  is Thr or Ser;

$Xaa_8$  is Ala, Ser or Thr;

$Xaa_9$  is Asp or Glu;

$Xaa_{10}$  is Ala, Leu or pentylglycine;

$Xaa_{11}$  is Ala or Ser;

Xaa<sub>12</sub> is Ala or Lys;  
Xaa<sub>13</sub> is Ala or Gln;  
Xaa<sub>14</sub> is Ala, Leu or pentylglycine;  
Xaa<sub>15</sub> is Ala or Glu;  
Xaa<sub>16</sub> is Ala or Glu;  
Xaa<sub>17</sub> is Ala or Glu;  
Xaa<sub>19</sub> is Ala or Val;  
Xaa<sub>20</sub> is Ala or Arg;  
Xaa<sub>21</sub> is Ala or Leu;  
Xaa<sub>22</sub> is Phe or naphthylalanine;  
Xaa<sub>23</sub> is Ile, Val or tert-butylglycine;  
Xaa<sub>24</sub> is Ala, Glu or Asp;  
Xaa<sub>25</sub> is Ala, Trp, or Phe;  
Xaa<sub>26</sub> is Ala or Leu;  
Xaa<sub>27</sub> is Ala or Lys;  
Xaa<sub>28</sub> is Ala or Asn;  
Z<sub>1</sub> is -OH,  
-NH<sub>2</sub>,  
Gly-Z<sub>2</sub>,  
Gly Gly -Z<sub>2</sub>,  
Gly Gly Xaa<sub>31</sub>-Z<sub>2</sub>,  
Gly Gly Xaa<sub>31</sub> Ser-Z<sub>2</sub>,  
Gly Gly Xaa<sub>31</sub> Ser Ser-Z<sub>2</sub>,  
Gly Gly Xaa<sub>31</sub> Ser Ser Gly-Z<sub>2</sub>,  
Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala-Z<sub>2</sub>,  
Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub>-Z<sub>2</sub>,  
Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub> Xaa<sub>37</sub>-Z<sub>2</sub> or Gly Gly  
Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub> Xaa<sub>37</sub> Xaa<sub>38</sub>-Z<sub>2</sub>;  
Xaa<sub>31</sub>, Xaa<sub>36</sub>, Xaa<sub>37</sub> and Xaa<sub>38</sub> are independently selected  
from the group consisting of Pro, homoproline,  
thioprolin and N-methylalalanine; and  
Z<sub>2</sub> is -OH or -NH<sub>2</sub>;

provided that no more than three of Xaa<sub>3</sub>, Xaa<sub>5</sub>, Xaa<sub>6</sub>, Xaa<sub>8</sub>, Xaa<sub>10</sub>, Xaa<sub>11</sub>, Xaa<sub>12</sub>, Xaa<sub>13</sub>, Xaa<sub>14</sub>, Xaa<sub>15</sub>, Xaa<sub>16</sub>, Xaa<sub>17</sub>, Xaa<sub>19</sub>, Xaa<sub>20</sub>, Xaa<sub>21</sub>, Xaa<sub>24</sub>, Xaa<sub>25</sub>, Xaa<sub>26</sub>, Xaa<sub>27</sub> and Xaa<sub>28</sub> are Ala; and pharmaceutically acceptable salts thereof.

20. A compound according to claim 19 which has an amino acid sequence selected from SEQ. ID. NOS. 6-19.

21. A composition comprising a compound of any of claims 1 to 19 in a pharmaceutically acceptable carrier.

22. A composition comprising a compound of claim 20 in a pharmaceutically acceptable carrier.

23. A method for the treatment of diabetes mellitus comprising the administration of a therapeutically effective amount of a compound according to claim 1.

24. A method for the treatment of diabetes mellitus comprising the administration of a therapeutically effective amount of a compound according to claim 18.

25. A method for the treatment of diabetes mellitus comprising the administration of a therapeutically effective amount of a compound according to claim 19.

26. A method for the treatment of diabetes mellitus comprising the administration of a therapeutically effective amount of a compound according to claim 20.

27. The method of claim 23 further comprising the administration of a therapeutically effective amount of an insulin.

28. The method of claim 24 further comprising the administration of a therapeutically effective amount of an insulin.

29. The method of claim 25 further comprising the administration of a therapeutically effective amount of an insulin.

30. The method of claim 26 further comprising the administration of a therapeutically effective amount of an insulin.

31. A method for the treatment of a hyperglycemic condition in a mammal comprising the step of administering a therapeutically effective amount of a compound according to claim 1.

32. A method for the treatment of a hyperglycemic condition in a mammal comprising the step of administering a therapeutically effective amount of a compound according to claim 18.

33. A method for the treatment of a hypoglycemic condition in a mammal comprising the step of administering a therapeutically effective amount of a compound according to claim 19.

34. A method for the treatment of a hypoglycemic condition in a mammal comprising the step of administering a therapeutically effective amount of a compound according to claim 20.

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35. A peptide compound of the formula (II) [SEQ. ID. NO. 66]:

Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Gly Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub>  
Xaa<sub>11</sub> Xaa<sub>12</sub> Xaa<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>15</sub> Xaa<sub>16</sub> Xaa<sub>17</sub> Ala Xaa<sub>19</sub> Xaa<sub>20</sub>  
Xaa<sub>21</sub> Xaa<sub>22</sub> Xaa<sub>23</sub> Xaa<sub>24</sub> Xaa<sub>25</sub> Xaa<sub>26</sub> X<sub>1-Z1</sub>; wherein

Xaa<sub>1</sub> is His, Arg or Tyr or 4-imidazopropionyl;  
Xaa<sub>2</sub> is Ser, Gly, Ala or Thr;  
Xaa<sub>3</sub> is Asp or Glu;  
Xaa<sub>5</sub> is Ala or Thr;  
Xaa<sub>6</sub> is Ala, Phe, Tyr or naphthylalanine;  
Xaa<sub>7</sub> is Thr or Ser;  
Xaa<sub>8</sub> is Ala, Ser or Thr;  
Xaa<sub>9</sub> is Asp or Glu;  
Xaa<sub>10</sub> is Ala, Leu, Ile, Val, pentylglycine or Met;  
Xaa<sub>11</sub> is Ala or Ser;  
Xaa<sub>12</sub> is Ala or Lys;  
Xaa<sub>13</sub> is Ala or Gln;  
Xaa<sub>14</sub> is Ala, Leu, Ile, pentylglycine, Val or Met;  
Xaa<sub>15</sub> is Ala or Glu;  
Xaa<sub>16</sub> is Ala or Glu;  
Xaa<sub>17</sub> is Ala or Glu;  
Xaa<sub>19</sub> is Ala or Val;  
Xaa<sub>20</sub> is Ala or Arg;  
Xaa<sub>21</sub> is Ala, Leu or Lys-NH<sup>e</sup>-R where R is Lys, Arg, C<sub>1</sub>-C<sub>10</sub> straight chain or branched alkanoyl or cycloalkylkanoyl;  
Xaa<sub>22</sub> is Phe, Tyr or naphthylalanine;  
Xaa<sub>23</sub> is Ile, Val, Leu, pentylglycine, tert-butylglycine or Met;  
Xaa<sub>24</sub> is Ala, Glu or Asp;  
Xaa<sub>25</sub> is Ala, Trp, Phe, Tyr or naphthylalanine;



Xaa<sub>26</sub> is Ala or Leu;

X<sub>1</sub> is Lys Asn, Asn Lys, Lys-NH<sup>e</sup>-R Asn, Asn Lys-NH<sup>e</sup>-R, Lys-NH<sup>e</sup>-R Ala, Ala Lys-NH<sup>e</sup>-R where R is Lys, Arg, C<sub>1</sub>-C<sub>10</sub> straight chain or branched alkanoyl or cycloalkylalkanoyl

Z<sub>1</sub> is -OH,

-NH<sub>2</sub>,

Gly-Z<sub>2</sub>,

Gly Gly-Z<sub>2</sub>

Gly Gly Xaa<sub>31</sub>-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser Gly-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub>-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub> Xaa<sub>37</sub>-Z<sub>2</sub> or

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub> Xaa<sub>37</sub> Xaa<sub>38</sub>-Z<sub>2</sub>; wherein

Xaa<sub>31</sub>, Xaa<sub>36</sub>, Xaa<sub>37</sub> and Xaa<sub>38</sub> are independently

selected from the group consisting of Pro,

homoproline, 3Hyp, 4Hyp, thioproline,

N-alkylglycine, N-alkylpentylglycine and

N-alkylalanine; and

Z<sub>2</sub> is -OH or -NH<sub>2</sub>;

provided that no more than three of Xaa<sub>3</sub>, Xaa<sub>5</sub>, Xaa<sub>6</sub>, Xaa<sub>8</sub>,

Xaa<sub>10</sub>, Xaa<sub>11</sub>, Xaa<sub>12</sub>, Xaa<sub>13</sub>, Xaa<sub>14</sub>, Xaa<sub>15</sub>, Xaa<sub>16</sub>, Xaa<sub>17</sub>, Xaa<sub>19</sub>, Xaa<sub>20</sub>,

Xaa<sub>21</sub>, Xaa<sub>24</sub>, Xaa<sub>25</sub>, and Xaa<sub>26</sub> are Ala; and pharmaceutically

acceptable salts thereof.

36. A compound according to claim 35 wherein Xaa<sub>1</sub> is His, Tyr or 4-imidazopropionyl.

37. A compound according to claim 36 wherein Xaa<sub>1</sub> is His.

38. A compound according to claim 36 wherein Xaa<sub>1</sub> is 4-imidazopropionyl.

39. A compound according to claim 35 wherein Xaa<sub>2</sub> is Gly.

40. A compound according to claim 35 wherein Xaa<sub>14</sub> is Leu, pentylglycine or Met.

41. A compound according to claim 35 wherein Xaa<sub>25</sub> is Trp or Phe.

42. A compound according to claim 35 wherein Xaa<sub>6</sub> is Phe or naphthylalanine; Xaa<sub>22</sub> is Phe or naphthylalanine; and Xaa<sub>23</sub> is Ile or Val.

43. A compound according to claim 35 wherein Z<sub>1</sub> is -NH<sub>2</sub>.

44. A compound according to claim 35 wherein Xaa<sub>31</sub>, Xaa<sub>36</sub>, Xaa<sub>37</sub> and Xaa<sub>38</sub> are independently selected from the group consisting of Pro, homoproline, thioproline and N-alkylalanine.

45. A compound according to claim 35 wherein Z<sub>2</sub> is -NH<sub>2</sub>.

46. A compound according to claim 35 wherein X<sub>1</sub> is Lys Asn, Lys-NH<sup>e</sup>-R Asn, or Lys-NH<sup>e</sup>-R Ala where R is Lys, Arg, C<sub>1</sub>-C<sub>10</sub> straight chain or branched alkanoyl.

47. A compound according to claim 35 wherein Xaa<sub>21</sub> is Lys-NH<sup>e</sup>-R where R is Lys, Arg, C<sub>1</sub>-C<sub>10</sub> straight chain or branched alkanoyl or cycloalkylkanoyl.

48. A compound according to claim 35 wherein said compound has an amino acid sequence selected from SEQ. ID. NOS. 67-74.

49. A composition comprising a compound of any of claims 35-47 in a pharmaceutically acceptable carrier.

50. A composition comprising a compound of claim 48 in a pharmaceutically acceptable carrier.